What Has Been Learned from Using EEG Methods in Research of ADHD?

Gráinne McLoughlin, Máté Gyurkovics, and Ümit Aydin

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Abstract Electrophysiological recording methods, including electroencephalography (EEG) and magnetoencephalography (MEG), have an unparalleled capacity to provide insights into the timing and frequency (spectral) composition of rapidly changing neural activity associated with various cognitive processes. The current chapter provides an overview of EEG studies examining alterations in brain activity in ADHD, measured both at rest and during cognitive tasks. While EEG resting state studies of ADHD indicate no universal alterations in the disorder, event-related studies reveal consistent deficits in attentional and inhibitory control and consequently inform the proposed cognitive models of ADHD. Similar to other neuroimaging measures, EEG research indicates alterations in multiple neural circuits and cognitive functions. EEG methods – supported by the constant refinement of analytic

G. McLoughlin (✉) and Ü. Aydin
Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
e-mail: grainne.mcloughlin@kcl.ac.uk

M. Gyurkovics
Beckman Institute, University of Illinois at Urbana-Champaign, Urbana, IL, USA

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strategies – have the potential to contribute to improved diagnostics and interventions for ADHD, underlining their clinical utility.

Keywords Electroencephalography (EEG) · Endophenotype · Error monitoring · Event-related potential (ERP) · Inhibitory control · Spectral composition

Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CEM	Cognitive-energetic model
CNV	Contingent negative variation
CPT	Continuous performance task(s)
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography (electroencephalogram)
ERN/Ne	Error-related negativity
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
IC	Independent component(s)
ISI	Inter-stimulus interval
MEG	Magnetoencephalography
NEBA	Neuropsychiatric EEG-based Assessment Aid
NIRS	Near infrared spectroscopy
Pe	Error positivity
Pre-SMA	Pre-supplementary motor area
RDoC	Research Domain Criteria
SCL(s)	Skin conductance level(s)
SMA	Supplementary motor area
TBR	Theta-beta ratio
VLF	Very low frequency (EEG)

1 Introduction

For almost 100 years, neurophysiological methods have been successfully applied to understand altered brain function in Attention-Deficit Hyperactivity Disorder (ADHD) (Jasper et al. 1938). The unparalleled temporal resolution of electroencephalography (EEG) can provide information on the strength, type and timing of the fast-changing cognitive processes that appear to be central to neurobiological understanding of the disorder. In this chapter, we introduce EEG methods and

review core findings related to ADHD. We further examine the evidence in the context of key neurobiological theories of the disorder. We also consider the impact of heterogeneity in ADHD on EEG-indexed neural activity and the role of EEG measures in explaining the heritability of the disorder. Finally, we close the chapter by discussing future perspectives in research on the neurobiology of ADHD.

2 Electromagnetic Imaging

Neuronal activity in the brain is associated with electrical currents that give rise to both electrical potentials on the scalp (measurable by means of EEG) and magnetic fields outside the head (magnetoencephalography/MEG). The EEG signal reflects the summated post-synaptic potentials of large populations of similarly aligned cortical pyramidal neurons (Luck and Kappenman 2011). MEG, on the other hand, records the magnetic field perpendicular to the electric field generated by the synchronously active neurons (Hari and Puce 2017). Both EEG and MEG measure the same underlying activity and they can provide information on the brain dynamics and temporal changes that are pertinent to understanding the abnormalities in sensory, cognitive and motor processing in ADHD. Both methods measure changes in synchronised cortical neuronal activity with millisecond precision, thus displaying the evolution of brain activity in real time. Consequently, they can be used to track covert, rapidly changing neural computations or changes in the cortex.

Despite measuring the same underlying activity, different sensitivity profiles of EEG and MEG make them complementary. MEG is mainly sensitive to quasi-tangential activity in the brain (activity on sulcal walls) while EEG is sensitive to both quasi-radial (sulci and gyri) and quasi-tangential sources. However, the signal to noise ratio for tangential sources is usually lower in EEG due to radially oriented background noise (Hari and Puce 2017). Because of these sensitivity differences, measurements might differ: e.g., some epileptic spikes could be visible only in EEG or MEG (Knake et al. 2006). It has been suggested that combined analysis of EEG and MEG might provide a better overview of the underlying activity and increase spatial resolution (Aydin et al. 2015; Baillet et al. 1999).

While the time courses of activations are critical in understanding brain function, it is also useful to know where in the brain signals of interest are generated. Spatial information from MEG and EEG is measurable in centimetres (especially without source localisation) and is thus less precise relative to other neuroimaging methods, such as functional magnetic resonance imaging (fMRI), which has a spatial resolution in the millimetre range and further has small co-registration errors as functional images can be superimposed on structural images. In contrast, with EEG and MEG the location of sources of activity in the brain could be estimated only after applying source localisation techniques to the sensor measurements. This estimation process is directly affected by volume conduction, which can create significant uncertainty regarding the localisation of EEG and MEG signals. One main difference between EEG and MEG is that the EEG source localisation is highly affected by the blurring

of the propagating electrical signal in space due to the low conducting skull; thus the signals measured on electrodes are a larger mixture of different sources, while MEG is mostly immune to this problem (Wolters et al. 2006; Aydin et al. 2014). However, recent major advances in computer hardware and signal processing are greatly increasing the amount of spatially precise information that can be extracted from EEG data using high-density channel recordings (Hari and Puce 2017; McLoughlin et al. 2014a).

Despite its importance as a neuroimaging method, MEG studies are comparatively rare in the literature due to the substantially higher cost of the method compared to EEG. In addition to its cost effectiveness, a further advantage of EEG is its portability and robustness to body movement relative to MEG. The development of dry, wireless, wearable, high density EEG systems makes the use of EEG in most recording locations feasible. Specifically, the lightweight EEG sensors and the lack of strict head movement constraints imposed by modern EEG recording and analysis methods allow accessible testing of developmentally young samples, a desirable approach for studies seeking to enable earlier detection of disorders (McLoughlin et al. 2014a; Lau-Zhu et al. 2019b). This brings a big advantage of EEG in comparison with fMRI, which requires restrictions on the movements of the participants during recording. In addition to the advantages mentioned above, EEG – and indeed, MEG – also has the benefit of being non-invasive in comparison with other neuroimaging measures, such as positron emission tomography that requires injection of radiotracers (McLoughlin et al. 2014a; Lau-Zhu et al. 2019b). These strengths and the ready accessibility of EEG have led to its proliferation in studies of neurodevelopmental disorders, including ADHD. Since MEG studies in ADHD are relatively rare, this chapter focuses on EEG.

3 Methods of Analysis

Due to its superlative temporal resolution, EEG is most commonly used to track the time course of various cognitive processes. The signal is a rich repository of temporal, spatial and spectral features that can be extracted using a variety of different techniques. In Fig. 1 we summarise the most common techniques for extracting meaningful information from the EEG signal (Tadel et al. 2011; Delorme and Makeig 2004). This is typically achieved in one of three ways.

First, the spectral composition of EEG signals can be quantified, for instance, by decomposing them into a set of cyclic waves of different frequencies and quantifying how much each wave contributes to the original signal. This process results in a spectrum of amplitude or power (squared amplitude) values across frequencies. This frequency domain representation of EEG is often investigated in resting-state studies when a person is not engaged in any specific task. Analyses are then commonly focused on the magnitude of power in one or more of the following canonical frequency bands: delta (<4 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (<30 Hz). Such narrowband power is typically interpreted as an

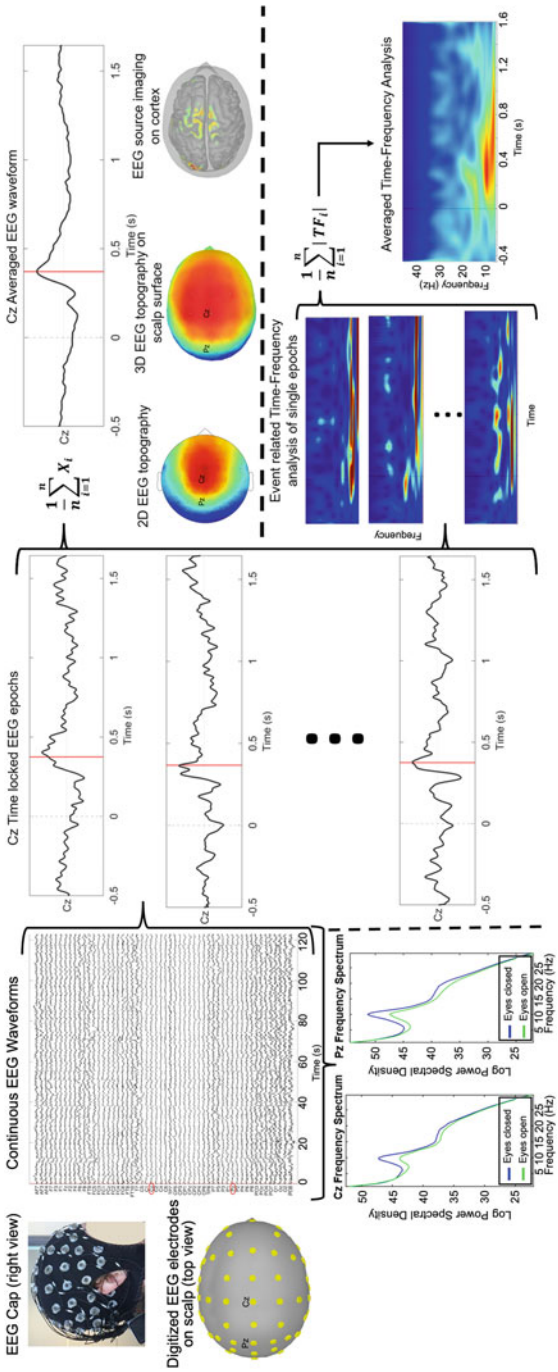

Fig. 1 (**a**) EEG data acquisition, digitization of the electrodes, and continuous EEG waveforms. (**b**) Spectral analysis of the continuous EEG waveforms to obtain the power in different frequencies for EEG channels Cz and Pz. Green line shows the spectrum with eyes closed and blue line shows for eyes open condition. Notice the attenuated alpha frequency (8–12 Hz) for the eyes open condition. Cz and Pz show different spectra especially for the alpha band. (**c**) In event related analysis continuous EEG waveforms are epoched using the event triggers. Here only the signals for the Cz channel are shown and the trigger used is the no-go events for the Continuous Performance Task (CPT). The time of the event trigger is shown as zero seconds. (**d**) Averaged event related potential (ERP) waveform for the Cz electrode with vertical red line showing the peak of the P3 component. (**e**) The spatial information at the peak of the P3 event is shown as 2D topography as well as 3D topography on the scalp. The EEG source imaging improves precision and allows the activity to be localised on the cortex. (**f**) Time-frequency analysis shows both time and frequency information. It is calculated for each epoch separately and then averaged to capture induced oscillations

oscillation at a frequency included in the specific band, although this may not always be justified and methodological care needs to be taken to ascertain that oscillations are indeed present (Wen and Liu 2016; Donoghue et al. 2020). In the case of resting-state data, the power across a range of frequencies is usually calculated at durations in minutes as opposed to milliseconds. The power in a particular frequency band can be expressed in absolute or relative terms, with relative power expressed as a percentage of power relative to all bands.

Secondly, event-related potentials (ERPs) reflect transient time- and phase-locked neural activity obtained by computing the average of the electrical potential in the range of milliseconds following or preceding some event. To do this, neural activity is typically recorded concurrently with a task and the data segments, or epochs, around task events of interest (e.g., the onset of a given stimulus) are aligned and averaged (Luck 2005). Activity that is consistently time- and phase-locked to the event across segments will be reflected in the average waveform, enabling the investigation of neuronal changes evoked by the event in the time domain. The functional significance of an ERP component is determined by its eliciting conditions (experimental variables), polarity (positive or negative), timing (latency) and spatial position (scalp distribution).

Finally, time and frequency domain information can be combined to yield the aptly named time-frequency domain representation of the data. This domain shows changes in the spectral composition (frequency domain representation) of neural activity as a function of time, typically following some task-relevant events, just like in ERP research (Herrmann et al. 2014; Cohen 2014). Time-frequency data allow researchers to draw conclusions about the time course of activity in different frequency bands (purportedly reflecting oscillatory activity). It also indicates how this activity changes in response to task events, compared to a (typically) pre-event baseline, showing stimulus- and task-related suppressions and enhancements. This helps link frequency bands to specific cognitive processes (i.e., those engaged by a given type of task event) and clarifies their dynamic interactions (Palva et al. 2005; Gratton 2018) (Fig. 1).

4 Resting State EEG

A body of quantitative EEG research highlights widespread alterations in resting state EEG in individuals with ADHD. The most consistent finding is an increase in slow wave, specifically theta, activity when compared with healthy controls, particularly with respect to frontal and central regions of the brain (Matsuura et al. 1993; Janzen et al. 1995; Chabot and Serfontein 1996; Lazzaro et al. 1998; Bresnahan et al. 1999) and, to a lesser degree, reduced faster-wave, beta activity (Mann et al. 1992; Clarke et al. 1998, 2001a, b; Lazzaro et al. 1998; Bresnahan et al. 1999; Bresnahan and Barry 2002). The combination of increased theta and decreased beta activity is sometimes quantified as the theta-beta ratio (TBR) and, when originally described by

Lubar in 1991, it was proposed to inversely index cortical arousal in ADHD (Lubar 1991). Support for the TBR as a biomarker of ADHD comes from multiple reports of more than 90% sensitivity and specificity (Monastra et al. 2001; Quintana et al. 2007; Snyder et al. 2008) and large effect sizes (>3.08) (Snyder and Hall 2006).

The theoretical link between TBR and cortical hypoarousal in ADHD was called into question by a series of studies that failed to show a link between TBR and objective measures of arousal (skin conductance levels, SCLs, Barry et al. 2004) and manipulations of arousal (caffeine, Barry et al. 2005). The role of TBR in the cognition of ADHD has, to date, been largely limited to exploration of its relationship to other EEG/ERP measures and its potential role in cognitive efficiency in ADHD (see below). Despite uncertainty about the theoretical implications of TBR, the evidence for its link with ADHD was sufficient for it to be approved as the first EEG biomarker of the disorder in 2013 by the United States Food and Drug Administration. The Neuropsychiatric EEG-Based Assessment Aid (NEBA) System (Saad et al. 2018) uses data from single electrodes at central and frontal locations to aid diagnosis of ADHD.

The announcement of NEBA has stimulated criticisms of the use of TBR in the diagnosis of ADHD. Studies have emerged that directly contradict its accuracy and reliability as a diagnostic biomarker in both children (Ogrim et al. 2012) and adults (Loo et al. 2009; van Dongen-Boomsma et al. 2010). A meta-analysis published in the same year as the NEBA release showed a significant association between TBR effect size and year of publication, showing a diminishing effect over time (Arns et al. 2013). This reduction in effect-size over time may be linked to the increase in rate of ADHD diagnosis, which the authors linked to false positives in the ADHD groups (reflecting overdiagnosis of the disorder in the population) (Snyder et al. 2015).

It is, however, important to note here that TBR in ADHD has remained stable over time and the diminishing effect size reflects an increase in TBR in the control samples (Arns et al. 2013). The largest study of the TBR in ADHD to date further failed to show an association between TBR and ADHD (Loo et al. 2013). The researchers behind NEBA propose that it should not be used as a standalone diagnostic tool but in conjunction with conventional diagnostic practices (Stein et al. 2016). This caveat notwithstanding, as growing numbers of practitioners incorporate its use into their patient assessments, further well-powered validation studies of the NEBA are required.

A critical point in resting state EEG studies of ADHD is the effect of age. Indeed, studies found that TBR was more effective at predicting age (up to 96.5% accuracy) than ADHD (up to 55% accuracy) (Buyck and Wiersema 2014; Liechti et al. 2013). The link between age and EEG variables is well-established: in general, slow wave EEG (i.e., delta, theta) decreases and fast wave EEG (i.e., alpha, beta) increases with increasing age (Benninger et al. 1984). A shift towards normalisation of beta activity in adult ADHD (Bresnahan et al. 1999, 2006; Bresnahan and Barry 2002; Hermens et al. 2004) was tentatively suggested to be related to the reduction in hyperactive-impulsive symptoms reported in adults with the disorder (Biederman et al. 2000);

however, a direct test of this hypothesis indicated that increased beta power is associated with a reduction in both attention and hyperactivity-impulsivity symptom domains (Loo et al. 2004).

Heterogeneity in ADHD, in Diagnostic and Statistical Manual (DSM) subtype/presentation, sex, age of onset and behavioural severity may also translate to variability in EEG profiles in ADHD. In contrast to decreases in higher-frequency activity (alpha and beta ranges) (Lazzaro et al. 1998; El-Sayed et al. 2002; Loo et al. 2009), other studies have found no differences (Bresnahan et al. 1999; Clarke et al. 2001a, b; Koehler et al. 2009; van Dongen-Boomsma et al. 2010) or even increases in these frequency bands (Chabot and Serfontein 1996; Clarke et al. 2011). Elevated beta activity was proposed as an EEG subtype of ADHD most common in the DSM-IV combined subtype (identical to DSM-5 combined presentation), representing 15–20% of this group (Clarke et al. 2001a, 2011).

A recent study by Loo et al. (2018) using a statistical method similar to cluster analytic techniques, called latent class analysis in a large sample, suggests five resting state subgroups in ADHD with differing patterns of associated behaviours and cognitive functioning. While the EEG subtypes loosely aligned with additional measures of behaviour, cognitive dysfunction, age and gender, crucially, the EEG subgroups were distributed in the same way across both ADHD and typically developing groups (Loo et al. 2018). This suggests that heterogeneity in brain function exists at the population level, rather than solely among children with psychiatric disorders, which is consistent with findings in ADHD using other neuroimaging methods and neuropsychological measures (Fair et al. 2012; Gates et al. 2014) and is furthermore in line with the dimensional approach of the Research Domain Criteria (RDoC) (Insel et al. 2010).

While there is limited evidence for consistent spectral differences between ADHD patients and non-affected individuals using resting EEG, these measures can be useful in tracking treatment response (Arns and Olbrich 2014), developmental outcomes (Clarke et al. 2011) and psychiatric comorbidities (Loo et al. 2018). Future research may need to consider individual differences in peak frequencies and thus the limitations of fixed frequency bands (Saad et al. 2018). A further consideration is the confounding effect of aperiodic, or in other words, non-oscillatory, background EEG activity on oscillatory measures, given emerging evidence linking the aperiodic component of EEG to ADHD and medication status (Robertson et al. 2019). Unless this aperiodic component is somehow accounted for, EEG ratio measures (including TBR), based on predefined frequency bands, could reflect changes in oscillations, the aperiodic component only, or a combination of both. This would create confusion about the meaning of the measured effect or, indeed, if the same effect is being measured across different studies. Further refinement of resting state EEG measures in combination with comprehensively described large samples is likely to lead to improvements in the understanding of the neurobiology of ADHD and also in the potential use of EEG in clinical settings.

5 Event-Related EEG

Event-related designs in EEG studies enable researchers to directly link spectral or amplitude changes in the recorded signal to cognitive processes. This can be done by using different cognitive tasks that tap into different domains of cognition: e.g., inhibitory control, working memory, cognitive flexibility. These tasks typically contain trials (or events), which engage the specific cognitive process or processes, and other trials that do not, or to a lesser extent. Electrophysiological changes that are unique to the former class of trials are then considered correlates of the cognitive process(es) in question. A common strategy for the understanding of brain pathophysiology across psychiatry, using all cognitive neuroscience methodologies, is to examine cognitive and neural dysfunction that is closely related to the core behavioural symptoms. Accordingly, the majority of event-related studies in ADHD aim to address questions focused on selective or sustained attention, inhibitory control and effort allocation (Johnstone et al. 2013), typically using variations of stop signal, flanker, go/no-go and continuous performance tasks (CPT) (Lau-Zhu et al. 2019a).

6 Inhibitory Control

One of the most established ERP findings in children and adults is that the P3, also known as the P300, in multiple contexts has been associated with the disorder (Kaiser et al. 2020). The P3 component is a positive voltage deflection occurring around 300 ms after a stimulus. When the P3 ERP is elicited by a stop signal or no-go stimulus, where a participant must refrain from making a prepotent or automated response, it is called the inhibition-related or no-go P3, and projects to frontal regions of the scalp (Fallgatter et al. 2002). A particularly robust finding is that ADHD is associated with a reduced amplitude and longer latency of the inhibition-related frontal P3 component (Lau-Zhu et al. 2019a; Kaiser et al. 2020). In the visual go/no-go task, a participant responds to a continuous stream of go stimuli (go trials), by pressing a button, but has to withhold a response when a no-go target appears (no-go trials). The go trials typically outnumber no-go trials to induce the prepotency of the go-response. Similarly, in the Stop Signal Task, a subject is asked to respond as quickly as possible to a stimulus but not to respond when a stop-signal (visual or auditory) follows the target stimulus.

These conditions elicit robust inhibitory processing and, in addition to the no-go P3, the no-go and stop stimuli evoke the frontal-midline N200 or N2, often together referred to as the N2/P3-complex (de Jong et al. 1990). The frontocentrally distributed N2 is a negative voltage deflection that peaks approximately 200–350 ms after a stimulus (Larson et al. 2014). However, in contrast to the no-go P3, the N2 is not consistently associated with ADHD (Kaiser et al. 2020). While the N2 was altered in ADHD patients in several studies (Pliszka et al. 2000; Barry et al. 2003; Albrecht

et al. 2008; Johnstone and Clarke 2009; McLoughlin et al. 2009; Wild-Wall et al. 2009; Rommel et al. 2019), there are exceptions (Overtoom et al. 1998; Banaschewski et al. 2004; Fallgatter et al. 2004; Spronk et al. 2008; Fisher et al. 2011; Tye et al. 2014). This discrepancy may relate to the respective functions of the N2 and the P3. Even though both have been described uniformly as indices of inhibition, it is now widely accepted that the N2 in fact reflects conflict detection and monitoring, 'the process of monitoring performance for simultaneously competing response options' (Groom and Cragg 2015; Hong et al. 2017). The inhibitory P3 is thought to reflect a 'braking' mechanism when inhibiting automated or prepotent response tendencies (Huster et al. 2013). Thus, while the N2 is elicited by these inhibitory conditions, unlike the no-go P3, it is not related to response inhibition per se, but rather reflects the conflict between the prepotent response tendency and the infrequent requirement to inhibit the response. In support of this, N2 amplitude for go trials increases when the ratio of go/no-go trials is reversed: an inversion that is not observed for the P3 (e.g., Enriquez-Geppert et al. 2010).

7 Error Processing

An ERP related to the N2 is the error-related negativity (ERN/Ne): a response-locked ERP occurring after the commission of errors. It has a strong negative frontocentral deflection that peaks 50–120 ms after erroneous responses (Falkenstein et al. 1990; Gehring et al. 1993). Source localisation and EEG-fMRI studies also suggest that the ERN and the N2 share common neural substrates in the medial frontal cortex, specifically the anterior cingulate cortex (ACC) and the pre-supplementary motor area (pre-SMA), despite their temporally distinct appearance in the processing of information, either prior to correct responses or after erroneous responses (Van Veen and Carter 2002; Yeung et al. 2004; Iannaccone et al. 2015).

EEG-indexed error monitoring has been found to be deficient in ADHD (Albrecht et al. 2008; Skirrow et al. 2009; McLoughlin et al. 2009; Geburek et al. 2013; Marquardt et al. 2018; Rommel et al. 2019; Michelini et al. 2021) although not in every study (Zhang et al. 2009; Wild-Wall et al. 2009; Groom et al. 2010) and a recent meta-analysis could not confirm an altered ERN in ADHD (Kaiser et al. 2020). The inconsistency in results could be explained by evidence that the N2 and ERN may be related to heterogeneity within samples in terms of age, IQ, ADHD presentation, medication status or comorbidities (Kaiser et al. 2020). Inconsistencies may also partially be due to differences in the type or degree of conflict engendered by tasks used in different studies (Brandeis et al. 2018). For instance, a large portion of studies that do find group differences in ERN magnitude use classic conflict tasks, such as the flanker task, whereas studies yielding null findings tend to use variants of the go/no-go task. Conflict stems from different stimuli priming incompatible responses simultaneously or quasi-simultaneously in the former, while it comes from the need to unexpectedly withhold a prepotent response tendency in the latter

task. While an early meta-analysis of the literature found evidence for a reduced ERN in ADHD using both tasks, this was based on a smaller set of studies (Geburek et al. 2013).

Nevertheless, a systematic investigation of how conflict type or task difficulty interacts with group differences in the magnitude of performance monitoring components is needed to address whether or not task design factors contribute to the heterogeneity of findings. Indeed, a recent study showed an interaction between the affective valence of task stimuli and the ERN in adult ADHD (Balogh et al. 2017). Furthermore, it is possible that time-frequency domain measures such as post-error phase and power dynamics, especially in the theta range, are more sensitive measures of performance monitoring than time-domain ERPs (Groom et al. 2010; Keute et al. 2019), leading to less stable findings in ERP studies. All in all, it appears that components related to performance monitoring (N2, ERN) are not reliably different in individuals with ADHD compared to healthy controls, or may be different only in a subgroup of these individuals.

Similar to the N2, the ERN is followed by a positive potential peaking at around 200-500 ms, known as the error positivity or 'Pe' (Falkenstein et al. 1990). The ERN is consistently observed when a mismatch occurs between representations of anticipated and actual responses, whereas the Pe appears to reflect error awareness (Falkenstein et al. 2000; Klein et al. 2007), reflecting conscious error processing or updating of the error context (Nieuwenhuis et al. 2001; Mathewson et al. 2005). Pe amplitudes are typically reduced in participants with ADHD compared to healthy controls and this finding is more consistent than the reduction in ERN (Kaiser et al. 2020). The Pe has been proposed to represent a P3-like facilitation of information processing modulated by sub-cortical arousal systems (O'Connell et al. 2007), which links with general deficits in P3 components in ADHD that may be modulated by arousal state (Wiersema et al. 2005, 2006).

8 Cognitive Models of ADHD

A highly influential theory places behavioural inhibition at the centre of cognitive dysfunction in ADHD (Barkley 1997). The model integrates neuropsychological and behavioural levels and proposes that inhibitory control is at the top of a hierarchy of self-regulatory behaviour in the disorder. In Barkley's model, the inability to inhibit or stop prepotent or on-going behavioural output interferes with normal functioning. This interference results in the development of further neuropsychological deficits in ADHD, specifically working memory, internalisation of speech and behavioural self-regulation of motivation, arousal and motor control (Barkley 1997).

Studies of inhibitory control in ADHD have typically operationalised this cognitive construct as the withholding of a prepotent or on-going response. Here, prepotent responses are actions that have previously been useful or reinforced, but that are not useful in the current situation owing to changes in the context, and on-going responses are behaviours that are already being executed and require interruption

(Barkley 1997). This operationalisation captures a form of cognitive control called reactive control, as it refers to situations where control processes are engaged following the onset of the target stimulus that requires a response. However, the evidence points towards this being too limited a model to explain the complex behaviours and altered brain function of ADHD. Poor inhibitory control can emerge due to dysfunctions in a number of processing stages: i.e., from the perceptual and attentional selection stage (Ocklenburg et al. 2011; Lackner et al. 2013; Grunewald et al. 2015) to the response selection stage (for a review, see Bari and Robbins 2013). This is because both perceptual processes (e.g., deficient attention) and response-related mechanisms (e.g., deficient inhibition) are crucial for adequate response inhibition. Rather than a central deficit of inhibitory control, event-related research in ADHD suggests that deficits exist on a number of these stages of action. In addition to the no-go P3, convincing and consistent evidence indicates reduced P3 amplitude to both go and cue stimuli within go/no-go and continuous performance tasks. In contrast to the anterior projection of the no-go P3 described above, these P3s are maximal over posterior scalp electrodes and reflect stimulus evaluation and response selection (P3b, Polich 2007). The 'go P3' is reduced in both children and adults with ADHD (Szuromi et al. 2011; Johnstone et al. 2013). Similarly, the P3 in response to predictive cues, which is maximal at posterior scalp sites, is also attenuated in ADHD in both children (Banaschewski et al. 2003) and adults (McLoughlin et al. 2010). A recent meta-analysis concluded that P3 components to all stimuli are the most sensitive ERP biomarkers of ADHD (Kaiser et al. 2020).

Additional cue processing deficits in ADHD are seen in the contingent negative variation (CNV), a frontocentral slow negative potential observed during the anticipatory interval after a cue stimulus. The same meta-analysis showed that reduced amplitudes of CNV were a consistent finding in over 52 studies of the disorder (Kaiser et al. 2020). Furthermore, cue-related deficits in ADHD are also indicated by a lack of cue-related suppression of alpha-band activity, which has been found in both children and adults with the disorder across a variety of tasks (for a review, see Lenartowicz et al. 2018). Suppression of alpha reflects increased control for processing upcoming stimuli via inhibition of irrelevant input (De Loof et al. 2019). In ADHD, these findings have been interpreted as deficient processing of the cue information prior to target onset, which may translate into impaired behavioural performance as well (Mazaheri et al. 2010).

The additional event-related deficits in ADHD, particularly for cue processing that precede the need for reactive control, indicate that a breakdown of inhibitory control is unlikely to be the central deficit in ADHD. Specifically, these findings suggest additional deficits in proactive control or the preparation of a reactive cognitive control network when it seems likely that reactive control may be required (de Zeeuw and Durston 2017). A recent study manipulated cues to either carry information about subsequent stimuli (e.g. to attend to a shape) or to simply alert the participant to a stimulus (with no task information). The aim was to tease apart whether reduced preparation in ADHD reflects proactive control impairments or is

the result of reduced general alerting in the disorder, as in general cues may both convey advance information about the task and also have a general alerting property. ADHD participants displayed alterations in the usage of informative cues to prepare for an upcoming task, indicative of a deficit in proactive control as opposed to general alerting (Sidlauskaite et al. 2020).

While these findings undoubtedly advance our understanding of the neurobiology of ADHD, alternative explanations remain possible in the context of the proposed cognitive models of ADHD. The dysregulation of downstream attention and perceptual systems in ADHD is consistent with another influential theory of ADHD, the cognitive-energetic model (CEM), which proposes that abnormalities in the regulation of basic information-processing may explain higher-order deficits in ADHD (Sergeant 2000). A central hypothesis of the CEM is that individuals with ADHD have difficulty in mobilising energetic resources and that this may be manipulated by specific task properties, including task difficulty and rewards. It is not clear if deficient alpha suppression in ADHD reflects a fundamental dysfunction in top-down frontoparietal circuitry or if this is a downstream problem with arousal (Lenartowicz et al. 2018). Consistent with the latter interpretation, reduced desynchronisation of alpha in ADHD is particularly pronounced during low working memory load conditions compared to high-load conditions (Lenartowicz et al. 2014). Similarly, larger effect-sizes are found for mean reaction-time, reaction-time variability and response accuracy in slower tasks (with long inter-stimulus intervals, ISIs) (Metin et al. 2012, 2016).

The periodic lapses of attention that are evident in ADHD during tasks with low event rates have alternatively been related to intrusions of the default mode network (DMN), known as the DMN interference model (Sonuga-Barke and Castellanos 2007). The DMN is typically deactivated during cognitive tasks and its activity is associated with mind-wandering and self-referential processing (Gusnard et al. 2001; Fox et al. 2015) and, as such, may interfere with appropriate task performance. While there is an inevitable degree of incongruence between hemodynamic and electrophysiological signals, researchers have proposed to examine DMN activity in ADHD using very low frequency (VLF) EEG (<0.2 Hz). VLF-EEG is increased in individuals with ADHD during the CPT and is associated with omission errors, an index of attention (Cooper et al. 2014). However, it has also been found to be decreased, though mainly during resting state (Helps et al. 2008, 2010). It is likely that EEG research has more to contribute to investigations of DMN interference in ADHD but, to date, has been bound by the observed weak to moderate correlations between EEG frequency domain features and regions associated with the DMN. Future research would benefit from an EEG-specific approach to identify correspondence between EEG features and known functional processes ascribed to the DMN (e.g., self-referential thought) and early work in this area is showing some promise (e.g., Bozhilova et al. 2020).

9 Heterogeneity in ADHD

As indicated in this chapter, and indeed, in this volume, the population of those affected by ADHD is heterogeneous, in terms of age, symptomatology, comorbidities and outcomes.

Defined according to the DSM-IV or DSM-5 (DSM), ADHD is also heterogeneous at the diagnostic level with three subtypes or presentations: primarily hyperactive-impulsive, primarily inattentive or a combination of both (combined presentation) (see Chapter "ADHD in Children and Adults: Diagnosis and Prognosis"). To date, limited evidence exists that the clinical presentations align with distinct neurobiological underpinnings. Early research taking this approach relied heavily on resting state EEG, which would provide clear potential benefits in ease of use in a clinical setting. The findings were often variable and lacked replication (for a review, see Loo et al. 2018). That limitation has justified an approach that extends beyond the clinical presentations of ADHD, using statistical clustering methods (e.g., latent class analysis, Loo et al. 2018), to derive subgroups based on neural activity (see Sect. 4, above: Resting State).

Recent work using event-related EEG measures hold more promise for uncovering differences between existing diagnostic presentations. For example, Mazaheri et al. (2014) provided some evidence that impaired suppression of alpha activity in task-relevant regions of the brain may be more typical of the inattentive presentation of ADHD, whereas those showing both inattentive and hyperactive symptoms displayed impaired suppression in the beta range, possibly suggesting poor motor planning during the preparatory period. Both groups, however, showed weakened functional connectivity between midfrontal theta activity and posterior alpha activity, which suggests a deficit in the top-down attentional control of perceptual processes after the cue across all subtypes/presentations of ADHD (Mazaheri et al. 2014).

Similarly, a series of studies examining differences in developmental outcomes in ADHD has indicated clear differences between those who persist with the diagnosis into adulthood and those who experience remission. Specifically, event-related theta power and phase was lower in those who have persistent ADHD while no differences in alpha suppression emerged between those in remission and those who retained the diagnosis (Vainieri et al. 2020). Event-related EEG data has also highlighted key differences in those with a single diagnosis of ADHD versus those who have a comorbid diagnosis. Investigations by Tye and colleagues indicate that those with ADHD have a different ERP profile compared with those who have a dual diagnosis of ADHD and autism spectrum disorder (ASD) with abnormalities in P3 amplitudes to cue and no-go stimuli evident in those with ADHD only (Tye et al. 2014).

The objective nature of EEG measurements and its ready availability in the clinic have led to work that aims to identify EEG subgroups. This work could lead to a personalised treatment approach based, in almost all cases, on the spectral contents

of resting state EEG recordings. Some of this work has indicated that EEG measures may be useful in predicting medication response. A 2014 review identified four different EEG subgroups based on their response to different medications (Arns and Olbrich 2014). Two subgroups (excess theta and high beta activity) were proposed to respond well to stimulant medication (Clarke et al. 2003b; Arns et al. 2008) whereas children with a slow individual alpha peak frequency were reported to be resistant to stimulant medication with poor outcomes (Arns et al. 2008). Another group was identified as having paroxysmal and epileptiform EEG, without the existence of seizures, and thus was suggested to have a good response to anticonvulsant medication (Silva et al. 1996). These findings suggest the potential for using EEG parameters for personalised medication in ADHD, but further research is required to confirm if, in practice, EEG subgroups could predict treatment outcome.

Event-related EEG approaches may hold more promise for tracking treatment response in ADHD. For example, in a large sample of medication naïve children with ADHD, Ogrim et al. (2014) conducted follow-up assessments after 4 weeks based on 23 parameters related to demography, IQ, DSM-IV subtype, as well as behavioural, ERP and EEG spectra parameters of a visual go/no-go task. They found that only three EEG parameters (amplitude of independent components (IC) representing cue P3 and no-go P3, and theta power) independently predicted a medication response as rated by clinicians blind to all EEG measures. Furthermore, in another study of IC amplitudes of the CNV, an early visual ERP as well as reaction-time were reported to predict side effects of medication (methylphenidate, Ogrim et al. 2013). Longer term neural changes have also been indicated by resting state EEG studies. Isiten et al. (2017) reported an increase in beta power after continuous use of methylphenidate for 1.5 years, in comparison with the EEG data prior to the treatment, and Clarke et al. (2003a) reported normalisation of theta, alpha and beta band EEG after 6 months of stimulant medication. Further work is required to investigate the long-term EEG correlates of medication use, including whether the reported effects are sustained after medication is ceased.

10 Endophenotypes: The Role of EEG in Explaining Heritability in ADHD

The heritability of EEG has long been investigated in twin and family studies (Vogel 1970). Consistent evidence indicates that the impact of genetic influences on EEG measures is moderate to high, similar to behaviour and brain structure measures, and surpassing heritability estimates found in twin and family studies of fMRI data (van Baal et al. 1998; Anokhin et al. 2004; Smit et al. 2005; Anokhin et al. 2006, 2008; Blokland et al. 2012). A meta-analysis in 2002 confirmed high heritability (50–80%) for frequency and ERP measures (van Beijsterveldt and van Baal 2002) indicating that they may have value as endophenotypes. An endophenotype is defined as a quantitative, subclinical and biological phenotype that is intermediate between the behavioural symptoms and genetic variation associated with the disorder.

Endophenotype studies aim to map neurobiological processes that mediate the relationship between behaviour, symptoms and genes (Ishii and Naito 2020).

Many studies have indicated that EEG/ERP variables share genetic or environmental variance with ADHD (Loo and Smalley 2008; Tye et al. 2012). A major requirement for an endophenotype is that it shows familial clustering with the disorder so that it is evident even in unaffected family members thus covarying with genetic vulnerability for the disorder even in the absence of symptoms (Gottesman and Gould 2003; Durston et al. 2009). In ERP studies of ADHD, familial segregation has been shown. Moreover, unaffected siblings or parents of individuals with ADHD display similar performance to those with the diagnosis across a range of executive control tasks (Albrecht et al. 2008; McLoughlin et al. 2009, 2011; Albrecht et al. 2013). For example, Michelini and colleagues investigated a large sample of adolescents and young adults with ADHD, their affected and unaffected siblings and controls on a range of tasks: familial influences on ADHD overlapped strongly with the ERN and the no-go P3 (Michelini et al. 2021).

Endophenotype investigations adopting strategies for advanced EEG analysis have had mixed results. A recent investigation aimed to predict ADHD symptoms using machine learning of connectivity signals across all canonical frequency bands (resting state EEG) in adults with the disorder, first degree relatives and healthy controls. While they found that EEG connectivity in specific frequency bands predicted hyperactive-impulsive and inattentive symptoms, separately, they failed to show a difference in any type of EEG connectivity measures between first degree relatives and healthy controls, thereby showing no familial clustering between the EEG measures and ADHD symptoms (Kiiski et al. 2020). Thus, the findings do not support network alterations as potential endophenotypes of ADHD. However, this may be because functional connectivity was analysed between electrodes (sensors) in this study, as opposed to between potential cortical sources of neural activity (Kiiski et al. 2020). In support of this notion, a study indicated that spatially-resolved cortical source measures of frontal-midline theta may share more genetic variance with the disorder than traditional scalp-based measures (McLoughlin et al. 2014b). The authors proposed that the improved signal-to-noise ratio of source imaging measures in EEG may provide a better representation of the underlying cortical activity and therefore may improve the ability to detect genetic effects on brain function measures and their overlap with the disorder. This approach was supported by a study showing an association between dopaminergic candidate genes and the go and no-go P3 in the source space, but not at the electrode (sensor) level (McLoughlin et al. 2018).

A key feature for any endophenotype, EEG-based or otherwise, is reliability in measurement and, in turn, statistical power to identify an association between the disorders and potential genetic causal factors (Iacono et al. 2017). ADHD, in common with all psychiatric disorders, is heterogeneous even at the genetic level and so the extraction of a common genetic background is a challenge (Faraone and Larsson 2019; McLoughlin et al. 2014a). Large studies are required to parse the neurobiological pathways, but these are potentially enabled by the use of advanced analysis methods and genetic approaches.

11 Future Directions

Future studies of the neurophysiology of ADHD could consider adopting novel methodologies and analytic approaches. In terms of methods, improvements in neuroimaging techniques provide powerful new tools for the investigation of the neural bases of ADHD. Recent advancements in MEG technology, such as optically pumped magnetometers that allow MEG sensors to be placed on the scalp, much like the EEG, improve the portability and resilience to movement (Boto et al. 2018; Hironaga et al. 2020). MEG is more sensitive to higher-frequency signals (i.e., gamma band activity) in the brain and these signals may be sensitive to alterations in emotional regulation in the disorder (Dor-Ziderman et al. 2021). Increasing evidence points towards emotional symptoms as a potential core feature of the ADHD diagnosis (Faraone et al. 2019; Biederman et al. 2020).

Further advantages arise from the use of optical techniques, such as near infrared spectroscopy (NIRS), which can be used to obtain hemodynamic information and has several clear advantages for studying children with developmental disorders, such as ADHD (Scholkmann et al. 2014). However, unlike fMRI, it measures both relative oxygenated and deoxygenated haemoglobin changes by measuring changes to the absorption of infrared light (Scholkmann et al. 2014). Furthermore, unlike fMRI, NIRS is silent and the acquisition environment is not intrusive, so it is a practical method for children with hyperactive symptoms. Although limited in number, to date, NIRS studies in ADHD have contributed to the understanding of the neurobiology of ADHD by pointing to hypo-metabolism in frontal brain regions during the go/no-go and Stroop tasks (Mauri et al. 2018). Furthermore, pharmacotherapy increased oxyhemoglobin in the prefrontal cortex (Nagashima et al. 2014; Ishii-Takahashi et al. 2015; Dolu et al. 2019; Grazioli et al. 2019). However, another study found increased prefrontal activity after treatment with atomoxetine, but not methylphenidate, even though participants receiving either medication showed a reduction of ADHD symptoms (Nakanishi et al. 2017). These studies included fewer than 60 participants and therefore studies with larger sample sizes are still needed. Perhaps one of the most important prospects is that EEG and NIRS could be measured simultaneously; analysing both sets of data would bring information on both direct neuronal activity and hemodynamics and so improve precision (Fazli et al. 2012; Shin et al. 2018; Dolu et al. 2019).

While resting state EEG investigations of ADHD have contributed to our understanding of the disorder, the interpretation of spectral changes is substantially more straightforward in event-related designs that target various, specific cognitive processes. Furthermore, event-related designs often permit researchers to link directly trial-to-trial fluctuations in neural activity with moment-to-moment variability in behaviour (e.g., accuracy or reaction-time) through single trial analyses (McLoughlin et al. 2014b). Such methodological, analytic and design considerations could help further uncover details of the neural basis of ADHD that have hitherto remained hidden or unclear. On-going advances in signal processing and visualisation of EEG activity could provide novel insights and/or more sensitive measures of

underlying cognitive processes in ADHD (McLoughlin et al. 2014a). Time-frequency decomposition of neural signals, particularly in the context of distinct cortical source activities, take advantage of the ability of EEG measures to both spatially and temporally characterise fast-changing events in the brain that are key to understanding the pathophysiology of ADHD.

The study of brain activity from EEG (and MEG) has benefited from the development of techniques that aim to characterise the degree of functional or effective brain connectivity between time series, in which cognitive functions are no longer associated to specific brain areas, but to networks of synchronously activated areas (Friston 2011). This approach reflects a shift from understanding the neurobiological basis of neurodevelopmental disorders, as focal brain abnormalities affecting specific systems, towards an overall pattern of brain reorganisation. While this research is still relatively underexplored in ADHD, initial investigations using this approach indicate disruptions in interrelated networks in ADHD (e.g., Pereda et al. 2018).

Together with machine-learning methods, these approaches can improve the predictive power of the proposed neurobiological models of ADHD and, consequently, may contribute to the development of screening and diagnostic tools. The importance of large sample sizes for such research is highlighted by a recent meta-analysis, which indicated that classification accuracies for ADHD appear to be inflated by small sample sizes that do not account for the heterogeneity in the disorder (Pulini et al. 2019). Furthermore, to achieve clinical benefits, machine-learning classifiers need to achieve good performance in independent samples: i.e., individuals not included in the original study. Brain connectivity research in fMRI has led the way in the validation of models in independent samples by indicating the value of validating all predictive models across independent data sets to identify a potential tool to assess attention independent of ADHD diagnosis (Yoo et al. 2018).

Although symptom-based diagnoses are the ‘gold-standard’ for clinical outcomes of ADHD, symptoms may be distinct from the actual burden of the conditions. Individuals with ADHD are at higher risk of experiencing a range of behavioural and functional problems, such as mood disorders, sleep problems and unfavourable psychosocial outcomes, including poorer academic performance and lower employment levels (Davidson 2008). Even individuals who no longer have the diagnosis but retain some symptoms have been shown to have lower work productivity, quality of life, functioning and self-esteem (Pawaskar et al. 2020). The role of cognitive dysfunction in the burden of ADHD over and above diagnosis has to date been under-researched. The use of cognitive biomarkers to predict and track outcomes – e.g., education, physical health, emotional and adaptive functioning – may have greater clinical impact than a focus on diagnosis alone by advancing the potential for personalised interventions. Such an approach could directly improve the lives of those affected by the disorder by improving wellbeing and quality of life.

12 Conclusions

As with other neuroimaging investigations of ADHD, EEG research has not been able to identify a final common pathway to the disorder. Nevertheless, this large body of research does show that, although there is limited evidence for universal alterations in ADHD, there are robust and consistent patterns emerging that incorporate these deficits in broader neurobiological frameworks: this applies particularly for P3 measures in multiple contexts and indices of proactive control, such as alpha suppression. Heterogeneity in ADHD and evidence that multiple neural circuits and cognitive functions are affected in the disorder have led to a preference for multiple pathway theories of the disorder that propose deficits in multiple, partially separable brain systems (Castellanos et al. 2006). Further insight into the neurobiology of ADHD is likely to be gained by large studies that take into account this heterogeneity and also take advantage of the rich information about cortical function provided by EEG data.

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